Introduction to Antibacterials

Introduction

Antibiotics technically means "anti anything living." Antibiotics generally refers specifically to antibacterials, drugs that fight infections by bacteria. Antivirals fight viruses and are discussed in the Virus series. Antifungals fight fungi and are discussed in the Fungus series. Antiparasitic medications will not be discussed in detail, simply listed in line when studying protozoa and helminths. Bacteria comprise the majority of the Microbiology module, and so it makes sense that antibacterial drugs comprise the most pharmacology in Microbiology. This introductory lesson lays out the antibacterial island, shows an overview of function, and discusses some general principles of antibiotic management. This series assumes you are comfortable with bacterial structure and function, and have completed the Bacteria series in this course. We do take the time to review key principles, but having intimate knowledge of bacterial structure, bacterial genetics, and which organisms are which Gram stain type will make this series much easier to comprehend.

Organization of the Antibacterial Series

We have categorized this series of content to be tailored towards the medications that target bacteria—Gram-positive organisms, Gram-negative organisms, and antimycobacterial agents. The series progresses from the outside in. Antibacterials #2: *β-Lactam Cell Wall Inhibitors* covers the cell wall synthesis inhibitors that are β-lactams. Antibacterials #3: *Cell Wall Inhibitors Not β-Lactams* covers the rest of the cell wall inhibitors and medications that affect the plasma membrane. Antibacterials #4: *Translation Inhibitors* discusses the multitude of drug classes that affect the bacterial ribosome and interrupt or prevent protein synthesis. Antibacterials #5: *DNA and RNA* covers medications that prevent nucleic acid synthesis or disrupt DNA or RNA directly. All of these lessons are about fighting Gram-positive and Gram-negative organisms. The Antibacterial series finishes with lesson #6: *Antimycobacterial*, which focuses on the management of tuberculosis and leprosy, introducing drugs that are essentially used only to treat mycobacteria.

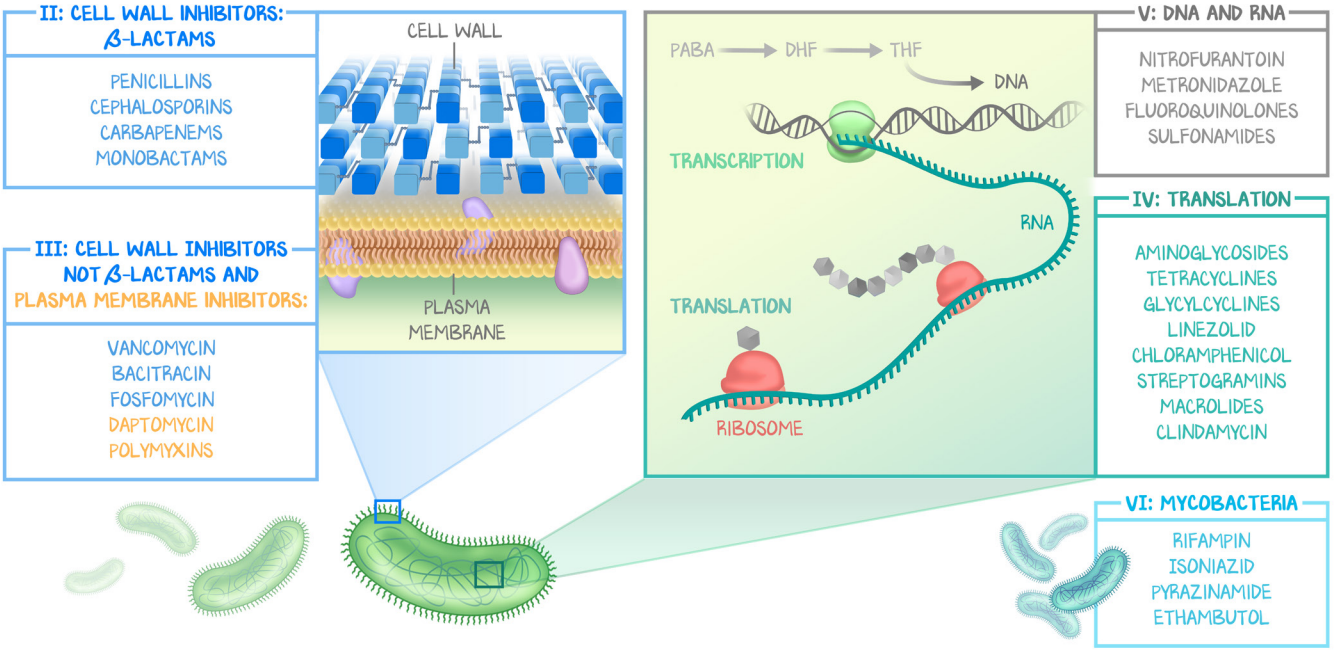

Figure 1.1: Mechanisms of Antibacterial Agents
The road map of classes and mechanisms of action for the rest of the Antibacterial series. Because bacteria are prokaryotic, there are multiple targets for therapeutics that will affect bacteria and not harm human cells.

We did not include summary tables of resistance patterns, classes with names, and the like, as many other texts do. You will have plenty of tables as you move through the series. Where appropriate, within each lesson and in the context of the drug or class being studied, we spend more time on resistance mechanisms or the mechanism of action of the drug. Where we don't spend time on it, you shouldn't be spending time on it. Critical features are discussed in tandem with the antibiotic or drug class in the given lesson. Tables are in the context of the lesson. Flashcards here are your friend.

This is a warm-up lesson that introduces some general principles of antibiotics and closes with the clinically relevant information contained in the antibiotic ladder, our model for empiric antibiotic selection.

Bactericidal and Bacteriostatic

Some antibiotics kill bacterial colonies; others arrest colony growth. You will need to be able to recognize both, either plotted on a graph or explained in words. Since bacteria grow by cell division, a colony will grow exponentially (one becomes two, two becomes four, four becomes eight, etc.). The exponential growth can be plotted on a graph, as shown in Figure 1.2. When a drug is administered, the response to that curve will indicate whether the drug is bactericidal or bacteriostatic.

Bactericidal drugs **kill bacteria**. They clear bacterial colonies quickly. The number of cells in the bacterial colony will decline after administration of a bactericidal antibiotic. If the drug is removed, the bacterial colony continues to decline in number. Bacteriostatic drugs **arrest growth**. This stops the bacterial cells from doubling, allowing the host immune system to take care of the job. If the drug is removed prematurely, the infection rears, all the bacteria still able to continue in the absence of the drug. These antibiotics may take longer to have a clinical effect. Upon administration, the number of cells in a colony will not change. Clearance of the infection is therefore reliant on the host immune system—the number of bacteria decrease only because the immune system kills them off while the bacteriostatic agent prevents new ones from growing.

If an infection is not completely cleared, that is, the bacterial quantity brought to zero, any remaining bacteria can pick up the torch and start doubling again. We have empiric evidence on the duration of antibiotic therapy for an infection. This discussion of bactericidal versus bacteriostatic is in reference to a single dose applied to a bacterial colony on a plate.

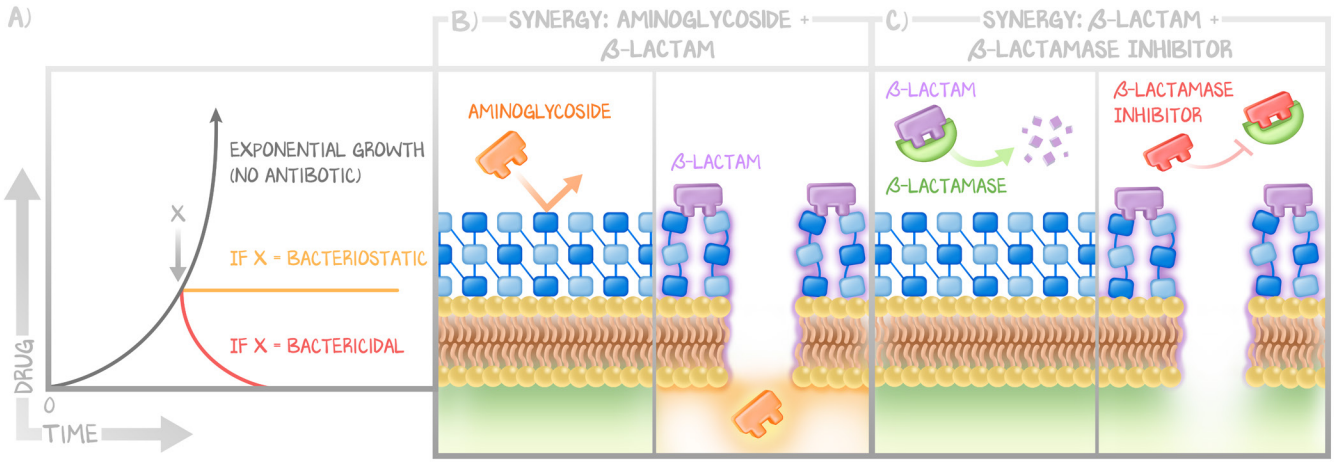

Figure 1.2: Bactericidal vs. Bacteriostatic
(a) The difference between bactericidal drugs and bacteriostatic drugs. Without antibiotics, bacteria grow at an exponential rate. Bactericidal drugs show a decline in the cells after administration; bacteriostatic drugs cause a plateau in cell division after administration. (b) Synergy between two drugs results in more potent antibacterial effect than the sum of the two drugs' independent effects. Synergy can be seen between two bactericidal antibiotics or (c) between an antibiotic and a drug that silences a mechanism of resistance.

Combining a **bacteriostatic** drug with a **bactericidal** would cause the opposite of synergy, **antagonism.** If one drug requires active protein synthesis (β-lactams) and another drug reduces protein synthesis (tetracyclines), there would be no substrate for the bactericidal drug to work on.

We are not discussing empiric coverage, where multiple antibiotics may be combined to cover a broader spectrum of organisms, as in the combination of ciprofloxacin (Gram-negative coverage) with metronidazole (anaerobic coverage) for an intestinal infection. Synergy occurs when two drugs are combined to more effectively kill one organism.

MIC and MIB

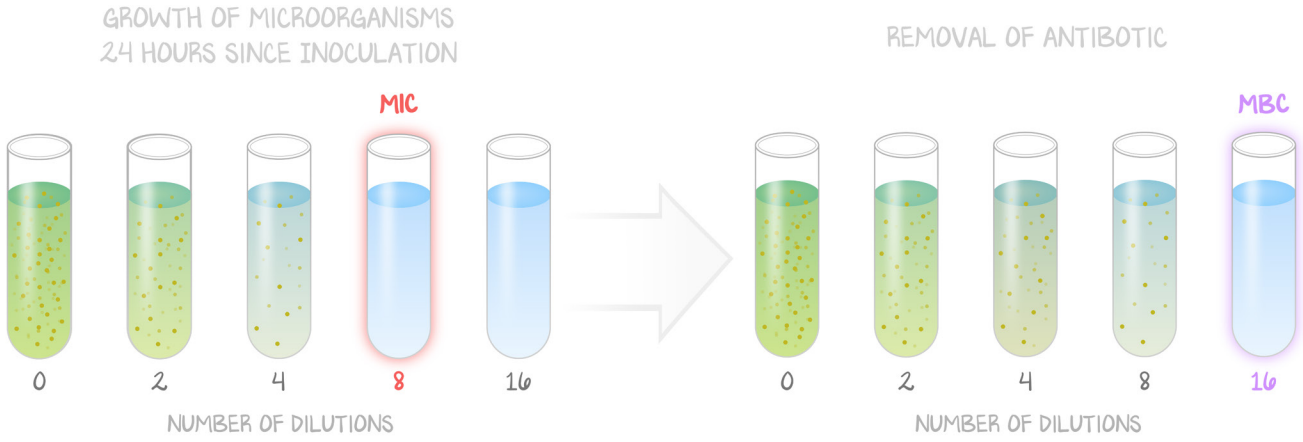

Figure 1.3: MIC and MBC
The minimum inhibitory concentration is the concentration of antibiotic at which no growth is seen at 24 hours. With removal of the antibiotic from the solution, the bacteria will continue to grow. The minimum bactericidal concentration is the concentration of antibiotic at which all cells die—removal of the antibiotic does not result in any cell growth.

The **mean inhibitory concentration (MIC)** is the lowest concentration of drug that **prevents visible growth** of a 24-hour incubation. A low MIC means greater sensitivity of that bacterium to that antibiotic—less drug is needed to kill. You **cannot compare different drugs' MICs to each other**. A lower MIC of one drug compared to another does not means the drug with a lower MIC is better than one with a higher MIC. The MIC is reported for multiple drugs on a single report, so the instinct is to compare. No. We have established serum concentrations for toxicity and efficacy (the therapeutic window) for each drug. We can use that historical data to determine whether this organism we are culturing and testing, our sample's bacterium, is "sensitive" (antibiotic good to use), "intermediate" (don't use unless combination therapy and special circumstances), or "resistant" (don't use this ever, it won't work) to the drug. We do that for multiple drugs at the same time. Drug serum levels should be 4–5 times the MIC to be effective. If the concentration required to kill the bacteria exceeds safe levels in humans, we can't use that antibiotic.

The **mean bactericidal concentration** is the lowest concentration of a drug that **results in 99.9% decline in colony count** after overnight incubation. This is rarely used in clinical practice and is not reported on culture and sensitivity data. But it illustrates a key feature of antibacterial principles. If an antibiotic is stopped too soon, even if it is bactericidal, the infection grows back. Killing all bacteria, not just killing enough that we can't see the colony with the naked eye, cures the infection. Proper antibiotic selection and complete duration of treatment cures infections. Poor choosing or stopping too soon breeds resistance.

Dosing

Some antibiotics exhibit a concentration-dependent effect, where more drug kills more bugs. Other antibiotics effect time-dependent killing, where increasing the concentration of the drug does not make it more effective at killing bugs. Increasing the concentration in a human—the drug is distributed to all tissues—is the only mechanism to increase the concentration affecting the bacteria in that human. However, rising concentrations get closer to toxic concentrations.

Concentration-dependent killing shows increase in the rate of bacterial death as the **dose** increases. The higher the concentration, the more bacteria die, and they die faster. This is how we think of most medications working—a small dose has a small effect; a large dose has a large effect. These medications benefit from **concentrated dosing** at intervals **fewer times per day**. These medications often have a dose-dependent side effect profile as well. Aminoglycosides and daptomycin exhibit this type of killing. The goal is to get the serum concentration many times higher than the MIC.

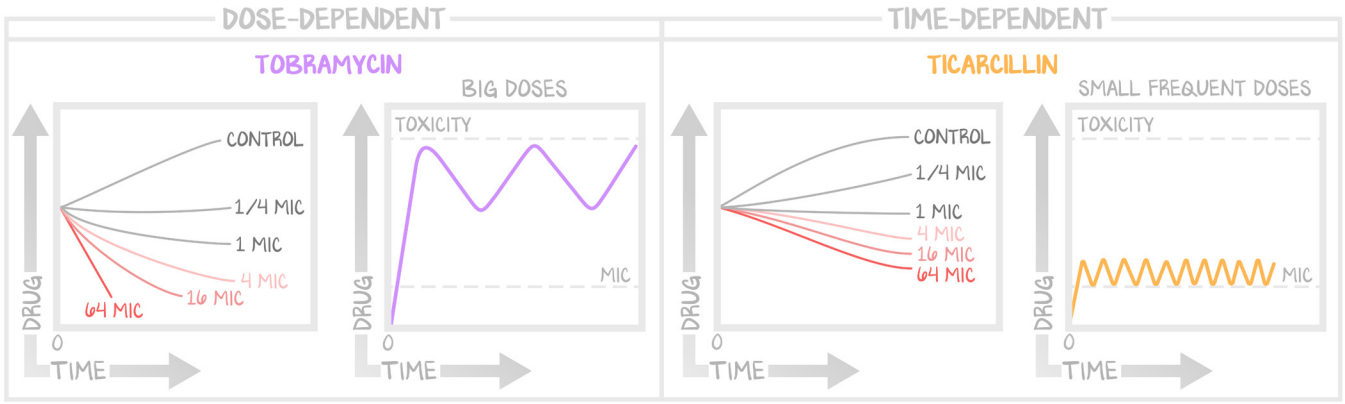

Figure 1.4: Concentration- vs. Time-Dependent Antibiotics
Tobramycin exhibits a concentration-dependent effect—more drug kills more bugs proportional to the increased dose. The bacterial numbers fall at a concentration 4-fold MIC and fall faster and lower at 64-fold MIC. Ticarcillin shows a concentration-independent effect, where the rate of bacterial killing does not significantly increase as the concentration exceeds 4- to 64-fold the MIC.

Time-dependent killing is also called **concentration-independent killing**. In this case, more drug does not mean more killing. The only thing that matters to these drugs is the **duration of time with serum concentrations above the MIC**. β-lactams, macrolides, and clindamycin exhibit this. Frequent, small doses keep the antibiotic at a serum concentration above MIC, but not much higher. Side effects do increase with increasing concentration, so getting the concentration in the human high not only fails to improve efficacy, it increases the likelihood of side effects. (Just don't forget that dosing is also dependent on rates of elimination and biotransformation, so the frequency of dosing isn't just based on time vs. concentration killing).

Postantibiotic effect is continued bactericidal activity even after the drug falls below the MIC. Fluoroquinolones and aminoglycosides exhibit this.

Selecting Antimicrobial Agents

The reality is that choice of antibiotics is often **empiric** based on the **diagnosis**. That is the case for **clinical practice**, where the **diagnosis** (cellulitis is skin infection, pneumonia is lung infection) **precedes organism identification**. Cultures may take two days to become positive. And while a **Gram stain** can shed some light, true **cultures and antibiotic sensitivities are required to tailor therapy**. For the basic sciences, your job will be to pick the antibiotic after being given the organism.

For empiric coverage, here are some simple rules.

1. If sick, go broad. If not sick, stay targeted. A person in septic shock gets "broad coverage," aka, "I don't know what's going on, but if I miss something, they die."

2. Escalate quickly. Infections kill people. Symptoms usually get better fairly quickly after initiation of antibiotics. They "defervesce" (fever, leukocytosis, toxicity, and symptoms should resolve within 24 hours). A failure to resolve or a worsening condition means you have the wrong bug, or that bug is resistant to that drug. Advance quickly.

3. De-escalate slowly. If you can't get a culture to tailor your antibiotics, and you want to start pulling back antibiotics, do so one at a time, day by day. If fevers appear or symptoms return, the one you just stopped is likely the one doing the good. And it isn't necessarily stopping an entire antibiotic, but de-escalating coverage of specific organisms (see the next section).

4. **Always use culture and sensitivity data to tailor antibiotics to the least-advanced antibiotic possible**. The more-advanced antibiotics are more clever, have more spectrum, or were created to get around a resistance type. They aren't "better." Exposing bacteria to those, when we could show them something weaker and simpler, will only hasten antibiotic resistance.

We illustrate this concept with the antibiotic ladder.

The Antibiotic Ladder

The antibiotic ladder is an overview of the different agents that are available to use for each type of infection. This is far less useful in the basic sciences than in the clinical sciences. We show you the antibiotic ladder and its accompanying images to give you the overview. The goal is to get the patient on the most focused, narrowed, lowest-on-the-ladder antibiotic. Antibiotic selection is often empiric at first. After cultures are drawn and sent to the lab, antibiotics are started based on the diagnosis. For two days, empiric coverage is what we use. It takes about 48 hours to get good sensitivities and organism identification. The link to diagnosis and empiric coverage is provided in the table that follows. Once the culture returns with an organism (with sensitivities), you should employ whichever antibiotic works and is low on the ladder. The higher up the ladder you go, the newer the antibiotic is. New, synthetic antibiotics are made to get around some resistance mechanism and are generally more toxic to patients. Using new antibiotics on a pansensitive organism only breeds resistance to the new synthetic. Get people on older, simpler antibiotics for organisms that have not developed resistance mechanisms.

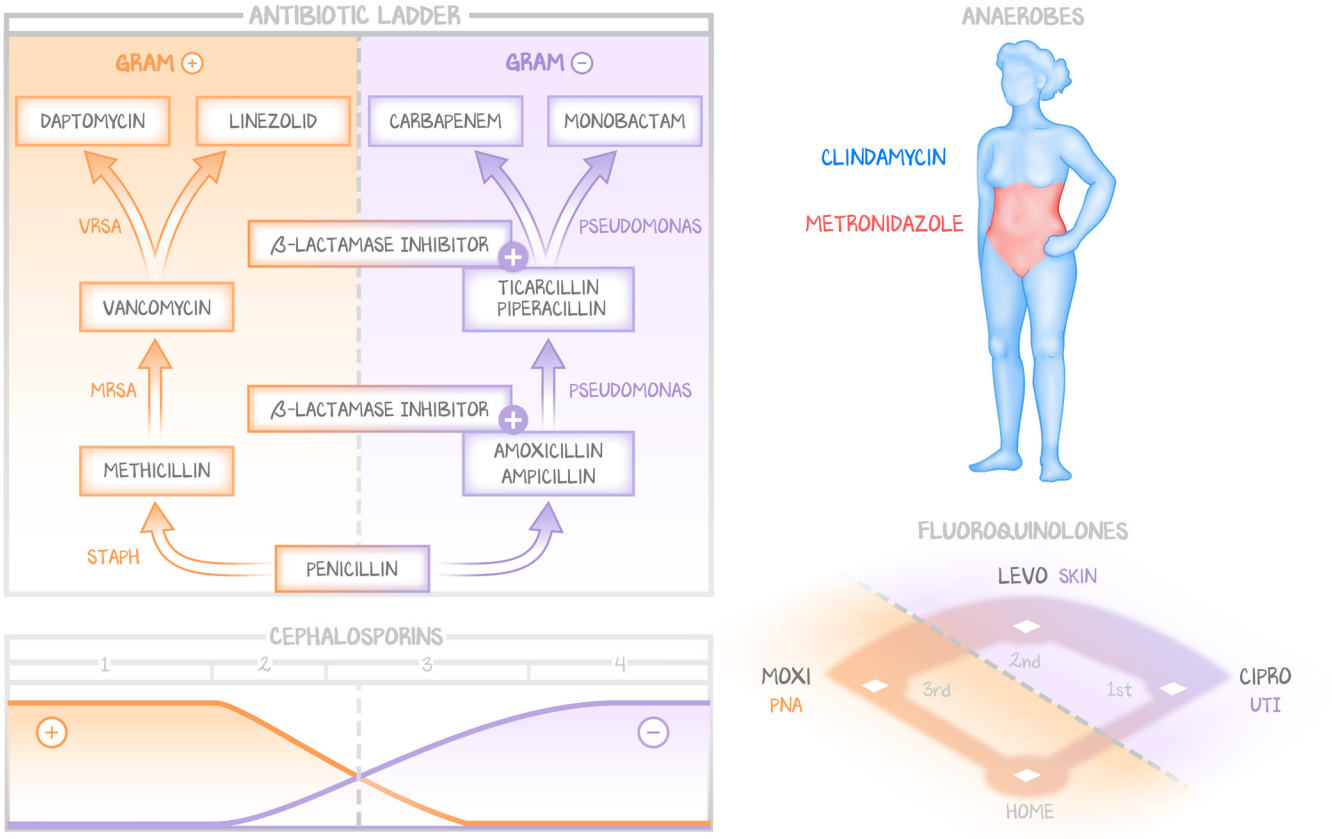

Figure 1.5: Antibiotic Ladder
The completed antibiotic ladder shows the path to cover Gram-positive organisms (especially *Staph. aureus*) and the path to cover Gram-negative organisms (especially *Pseudomonas*). The higher up the ladder, the more advanced the antibiotic. Notice that it is "more advanced" and not "bigger gun." When treating empirically, use the best-practice evidence (see the table below). When treating with a culture and sensitivity, always choose the lowest on the ladder possible. The ladder's foundation is the cephalosporins. The earlier generations treat Gram-positive organisms. The later generations treat Gram-negative organisms, with the most recent fourth-generation treating *Pseudomonas*. In addition, there is anaerobic empiric coverage (metronidazole is abdomen, pelvis, vagina; clindamycin is everywhere else). And finally there is the baseball diamond, the organizer to remind you that ciprofloxacin, the earliest, covers Gram negatives; moxifloxacin, the newest, covers Gram positives; and levofloxacin doesn't matter.

UTI	PNEUMONIA	CELLULITIS	GUT INFECTIONS
Amoxicillin (UTI)	Ceftriaxone + azithromycin	Ceftriaxone (non-staph)	Ciprofloxacin + metronidazole
Nitrofurantoin (PCN all)		Vancomycin (staph)	
Ceftriaxone (Pyelo)	Moxifloxacin		

Table 1.1: Empiric Coverage of Infections